Journal of Pharma Research
Available online through
www.jprinfo.com

Research Article
ISSN: 2319-5622

Formulation and *In-Vitro* Evaluation of Gastro Retentive Tablets of Cefpodoxime Proxetil

[1]Arbind Baniya, [1]Bhupendra Kumar Poudel*, [2]Anita Yadav, [2]Manju KC, [2]Sudip Prajapati, [2]Vijay Khatri, [2]Asgar Ali Mikrani

[1]Department of Drug Administration, Government of Nepal; [2]Crimson College of Technology, Pokhara University.

Received on: 25-05-2015; Revised and Accepted on: 02-06-2015

ABSTRACT

The present work attempts to formulate gastro retentive Cefpodoxime Proxetil using gas generating technique wherein solid dispersion and physical mixture of Cefpodoxime Proxetil were prepared using PEG-6000 and Ethanol by solvent evaporation. Solid dispersion (having greater saturation solubility, pH dependent solubility, percent drug content and in vitro dissolution) was prepared by wet granulation, employing gas generating agents (Sodium Bicarbonate and Citric Acid), water soluble polymer (HPMC K-15 M and Xanthan gum or Ethyl cellulose and Xanthan gum), binder (PVP K-30 in isopropyl alcohol) and Talc & Magnesium stearat. Prepared tablets were characterized for in-vitro buoyancy, physicochemical properties and in vitro release. The results showed Solid dispersion (SD2) prepared with 1:1 ratio of drug and PEG-6000 enhanced saturation solubility by 42.88%, pH dependent solubility in 0.1N HCl by 90.53% and in PBS (pH 7.4) by 83.87% in comparison with pure Cefpodoxime Proxetil. Maximum % dissolution (92.35%) of Cefpodoxime was observed in SD2 as comparison to physical mixture (78.04%) and pure drug (37.19%) at 60 minutes. Gastro retentive tablets prepared with HPMC K-15M remained floated for more than 12 hours. Formulation (prepared with 15% of HPMC K-15M showed maximum drug release (90.04%) at 8 hour with minimum fluctuation in release pattern. Hence, using Solid dispersion technique with PEG-6000, solubility of Cefpodoxime gastroretentive tablets can be increased.

Keywords: *Cefpodoxime Proxetil, Solid Dispersion, Gastro Retentive Tablet, Solubility.*

INTRODUCTION

Cefpodoxime proxetil (CP) is an orally administered, extended spectrum, semisynthetic antibiotic of the Cephalosporin class. It is a prodrug and its active metabolite is Cefpodoxime [1]. It has very good in vitro activity against *Enterobacteriaceae, Hemophilus species*, and *Moraxella species,* including lactamase producers and many strains resistant to other oral agents [1] and is active against any Gram-positive and gram-negative bacteria [2]. It is stable and well absorbed within pH range 1-4. Above pH 4 it undergoes hydrolysis to form active Cefpodoxime. But the active metabolite Cefpodoxime is not absorbed from gastrointestinal tract. So the bioavailability of Cefpodoxime proxetil may be increased by reducing its hydrolysis [3]. The short half life of CP (2-3 hours) suggests that it is rational drug for sustained drug delivery. The high solubility, chemical and enzymatic stability and absorption profile of CP in acidic pH values (of stomach), points to the potential of gastro retentive dosage form [4]. Therefore, the main objective was to prepare gastro retentive CP by using gas generating technique with an inert solid carrier and gas releasing material to improve the oral bioavailability of poorly water-soluble drug Cefpodoxime proxetil.

MATERIAL AND METHODS

Cefpodoxime proxetil (Potency 100% and Moisture content 1.4676%) was provided by Asian Pharmaceuticals Pvt. Ltd, Padsari, Rupandehi, Nepal. Hydroxyl Propyl Methyl Cellulose (HPMC K-15M), Ethyl cellulose, Starch, Polyvinylpyrrolidone (PVP K-30), Citric acid, Purified Talc and Magnesium Stearate were provided by Siddhartha Pharmaceuticals Pvt. Ltd, Madhwaliya, Nepal. Two marketed Samples: Sample1 (Cedon 100 DT, Blue Cross) and Sample2 (Microcef 100DT, Micro Lab) were purchased from local retail pharmacy.

***Corresponding author:**
Bhupendra Kumar Poudel
Department of Drug Administration,
Government of Nepal. Phone: +9779841380139, Fax: 014780572
**E-Mail: poudel.bhupen@gmail.com*

Preparation of Solid Dispersions (SDs) by Solvent Evaporation and physical mixtures (PM):

It was prepared by solvent evaporation method using PEG-6000 in different weight ratios of 1:0.5, 1:1, 1:1.5, and 1:2 of drug: carrier polymer [5] in ethanol and stirred. Solid dispersions thus formed, were then dried in hot air oven for 24 hrs at the temperature 40°C, pulverized and sieved through sieve no. 60. Physical mixtures were prepared by mixing appropriate amounts of the drug and carrier PEG-6000 in the different weight ratios of 1:0.5, 1:1, 1:1.5, and 1:2 and were sieved through sieve no. 60 and stored [6].

Evaluation of Prepared SDs and PMs:

Saturation solubility was determined by using shake flask method [6]. Excess quantities of pure CP, prepared SDs and PMs were added in 25 ml distilled water in conical flasks which were then shaken, sonicated, filtered and then absorbance was taken at 259 nm. For shake flask method same as that for saturation solubility was used with 0.1N HCl and phosphate buffer saline (pH 7.4) as solvents for determining pH dependent solubility.

Percent Drug Content:

SDs equivalent to 100 *mg* of Cefpodoxime to 100 *mg* cefpodoxime was dissolved and diluted up to 100 *ml* with acidified ethanol to prepare stock solution, sonicated, filtered filtered and drug content determined by measuring absorbance at 264.3 *nm.*

***In Vitro* Dissolution Studies:**

In vitro dissolution studies of prepared SDs were carried out in 900 ml of Glycine medium using USP type 2 test apparatus with 75 rpm and temperature of 37±0.5°*C*. At 15 minutes samples were analyzed at 259 *nm* after quantitative dilution**.**

Preparation of gastro retentive (floating) tablets:

Floating tablets containing SDs of CP and carrier at the ratio of 1:1 complex were prepared by a conventional wet granulation method, employing starch as diluents, sodium bicarbonate and citric acid as gas generating agent and water soluble polymer (HPMC K-15M and Xanthan gum or Ethyl cellulose and Xanthan gum) as hydrophilic matrix. All ingredients were mixed and passed through sieve 60 thoroughly except Sodium Bicarbonate, Citric Acid, Magnesium Stearate and purified Talc. Granules were

prepared manually with a solution of the 1.5% Polyvinylpyrrolidone (PVP K-30) in sufficient Isopropyl alcohol as binder. The dried granules were passed through sieve mesh size 30 and mixed with remaining ingredients and compressed using 20 station Tablet Compression Machine (CPMD-3) using 12 mm flat faced punches to obtain the tablets at controlled environment (23°C Temperature and 75% Relative Humidity) in tablet section of Universal Formulation Pvt. Ltd Chilhiya, Rupandehi, Nepal. Prior to compression, granules were evaluated for fluidity and compressibility by measurement of angle of repose, bulk density, tapped density and compressibility/ Carr's index. Total eight batches with batch size 570 tablets were prepared.

Table No. 1: Composition of different formulation of gastroretentive tablets.

	Formulation Code							
Ingredients (in *mg*)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Solid Dispersions	230.45	230.45	230.45	230.45	230.45	230.45	230.45	230.45
Starch	89.7625	63.5125	37.2625	11.0125	89.7625	63.5125	37.2625	11.0125
Ethyl cellulose	26.25	52.5	78.75	105	-	-	-	-
HPMC K-15M	-	-	-	-	26.25	52.5	78.75	105
Xanthan gum	50	50	50	50	50	50	50	50
Sodium Bicarbonate	75	75	75	75	75	75	75	75
PVPK-30	7.7875	7.7875	7.7875	7.7875	7.7875	7.7875	7.7875	7.7875
Citric acid	30	30	30	30	30	30	30	30
Talc	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
Magnesium Stearate	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
Total wt. (*mg*)	525	525	525	525	525	525	525	525

The pre compression parameters like angle of repose, compressibility index, hausner's ratio, tapped and bulk density were evaluated and the *in vitro* buoyancy studies performed. Randomly selected tablets from each formulation were kept in a 500ml beaker containing 0.1 N HCl which is equivalent to simulated gastric fluid, pH 1.2 as per USP at 37 °C. Floating Lag Time (FLT) and Total Floating Time (TFT) were calculated. The post compression parameters like thickness, diameter, hardness, weight variation and friability dissolution and assay were determined.

Then assay was calculated as:

$$\text{Assay \%} = \frac{\text{Spl. Abs}}{\text{Std. Abs}} \times \frac{\text{Std. Wt}}{\text{Spl. Wt}} \times \frac{\text{Spl. dilution}}{\text{Std. dilution}} \times \frac{100 - \text{LOD}}{100} \times \text{Purity \% ..... (11)}$$

Spl. Abs = Absorbance of the sample.
Std. Abs = Absorbance of the standard.
Std.Wt = weight of standard.
Spl. Wt = weight of sample.
LOD = loss on drying.

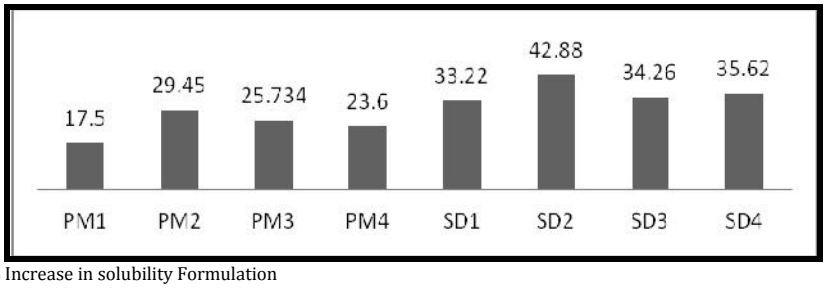
Statistical Evaluation:

Method validation and regression analysis was performed by using MS-Excel 2007 and Statistical Package for Social Sciences (SPSS) v 16.

RESULTS

Calibration curves revealed correlation coefficient (R^2) value of Cefpodoxime to be 0.996. The spectrum of highest absorbance for Cefpodoxime was absorbed in between 235 -365nm which shows the highest absorbance at 264.3 *nm* at concentration of 10 *µg/ml*. The accuracy performed in different concentration of sample shows result near to the true value. The mean percentage recoveries ranged from 98.97±0.2987. These values are very close to 100, indicating the accuracy of the proposed method. Relative standard deviation (RSD) of the sample done in accuracy test was found as 0.52278 % which was less than 2% which signifies this method is precise. The limit of detection was found 0.0985*µg/ml.* The Limit of Quantitation was found to be 0.298*µg/ml*. No interference was exhibited by the excipients in the spectroscopic analysis with the developed method.

Determination of Saturation Solubility:



% Increase in solubility Formulation

Fig. 1: Saturation solubility of PMs and SDs.

As shown, all PMs showed higher saturation solubility as compared with pure CP but higher solubility in the case of formulation SD2 (1:1 ratio) so, PEG-6000 enhances the aqueous solubility at the ratio of 1:1(drug: PEG-6000).

Determination of pH Dependent Solubility:

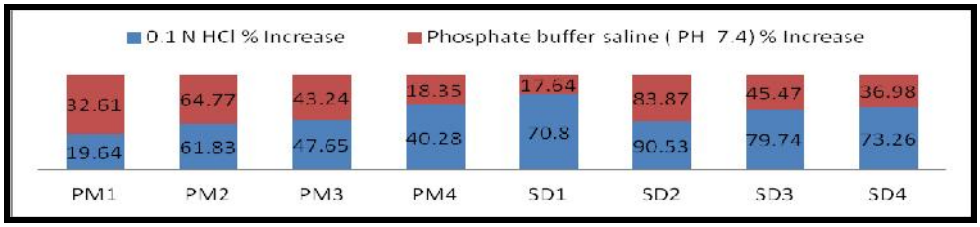


Fig. 2: pH Dependent Solubility of PMs and SDs

As shown, all PMs showed higher pH dependent solubility as compared with pure CP and higher in the case of formulation SD2 (1:1 ratio).

Percent Drug Content:

Table No. 2: Percentage content of drug in PMs and SDs

Formulation	% Content
PM1	88.01
PM2	90.92
PM3	86.68
PM4	82.75
SD1	99.12
SD2	99.87
SD3	98.03
SD4	98.59

Table No. 3: Dissolution % of CP, PMs and SDs at specified time interval

Formulation	15 min	30 min	45 min	60 min
CP	18.6	24.8	30.3	37.19
PM2	45.56	60.42	70.07	78.04
SD2	50.78	71.34	84.04	93.35

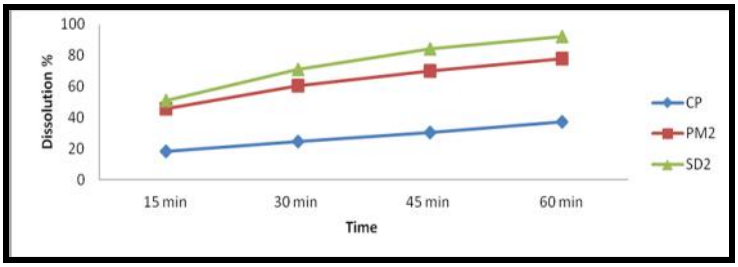


Fig. 3: Comparative Dissolution Profile of CP, PM2 and SD2

The above figure indicates that solid dispersion of Cefpodoxime Proxetil prepared by solvent evaporation method using PEG-6000 enhance the dissolution of the drug.

Result of various pre-compression parameters of gastro retentive formulation:

Table No. 4: Pre-compression Parameter of granules

Formulation	Angle of repose (θ)	Bulk density (*g/ml*)	Tapped density (*g/ml*)	Compressibility (%)	Hausner's ratio
F1	21.8	0.645	0.709	9.027	1.099
F2	23.62	0.63	0.696	9.433	1.105
F3	23.62	0.702	0.769	8.743	1.095
F4	26.56	0.63	0.702	10.256	1.114
F5	23.94	0.69	0.769	10.273	1.114
F6	23.57	0.68	0.762	10.761	1.121
F7	29.57	0.71	0.8	11.25	1.127
F8	26.46	0.63	0.708	11.017	1.124

Table No. 5: *In vitro* Buoyancy determination studies

Formulation	Floating Lag Time (FLT)	Total Floating Time (TFT)
F1	64 sec	10 hrs
F2	1 min	8 hrs
F3	1 min 23 sec	10 hrs
F4	41 sec	10 hrs
F5	3 min 44 sec	>12 hrs

F6	1 min 53 sec	>12 hrs
F7	1 min 17 sec	>12 hrs
F8	39 sec	>12 hrs

Table No. 6: Physicochemical properties of gastro retentive tablets

Formulation	Weight variation (*mg*) Mean±SD (n=20)	Thickness (*mm*) Mean±SD (n=10)	Hardness (kg/cm²) Mean±SD (n=10)	Friability (%)	Drug content (%)
F1	524.26±2.61	4.79±0.0233	5.98±0.108	0.036	86.15
F2	518.29±2.71	4.77±0.0366	5.43±0.068	0.276	90.58
F3	522.28±3.49	4.80±0.0298	5.45±0.050	0.315	91.02
F4	526.51±2.17	4.78±0.0290	5.34±0.049	0.151	88.15
F5	518.54±1.77	4.69±0.0378	5.37±0.068	0.277	95.44
F6	519.51±2.8	4.82±0.0290	5.39±0.0504	0.019	96.54
F7	529.05±3.00	4.78±0.0290	5.40±0.053	0.676	93.67
F8	525.87±2.69	4.77±0.0213	5.39±0.052	0.53	93

Table No. 7: Percentage Drug Content in Tablets

Formulation	% Drug Content
F1	86.15
F2	90.58
F3	91.02
F4	88.15
F5	95.44
F6	96.54
F7	93.67
F8	93

Table No. 8: Release pattern of drug from different formulation at specified time intervals

Time	F1	F2	F3	F4	F5	F6	F7	F8
30min	4.76	4.21	4.11	3.35	7.44	4.06	5.8	4.07
1 hr	7.73	6.94	7.16	8.8	10.44	7.7	9.22	8.91
2 hr	32.28	11.56	17.3	15.2	15.53	13.43	16.89	15.36
3 hr	42.86	20.3	26.7	27	30.57	27.61	35.26	26.9
4 hr	55.83	27.5	35.05	47.85	41.7	39.71	42.06	48
5 hr	60.27	33.22	38.44	53	57.17	58.71	54.3	52.7
6 hr	72.83	40.5	46.1	57.1	62	71.68	61.05	58.7
7 hr	77	57.61	49.14	66.8	70.63	81.2	70.92	65.67
8 hr	80.87	75.95	72.1	85.3	84	90.04	87.81	86.06

DISCUSSION

The active ingredient and excipients did not interfere in the estimation [7]. The solubility data of Cefpodoxime Proxetil reveals that it is poorly soluble in water [8]. Mechanisms of increased dissolution are improved wettability, reduction of crystal size, absence of aggregation of crystalline drug and conversion of drug from crystalline to amorphous state [9]. SDs prepared in 1:1 ratio of CP and PEG-6000 showed maximum increase in saturation solubility, P^H dependent solubility and *in vitro* dissolution profile so same composition i.e. 1:1 was selected for the preparation of physical mixture. The observed increase in the solubility of CP in solid dispersion may be due to solubilization effect of the PEG-6000 and formation of concentrated diffusion layer [10]. There are reports that say PEG-600 results prolonged release of drug and increase in solubility and bioavailability [11]. It was found that the drug release from physical mixture is greater than that of the pure drug and slower than that of solid dispersions. From the results, it was conclude that the dissolution rate of Cefpodoxime Proxetil increased by preparing solid dispersion.

CONCLUSION

Gastro retentive tablets of Cefpodoxime Proxetil prepared using 15% HPMC K-15M achieve an extended retention in the upper GIT with best *in vitro* release. Further, SD2 showed better dissolution when compared with the pure CP and its respective PM which when used to prepare gastro retentive tablet. From these we concluded that gastro retentive drug delivery system for Cefpodoxime Proxetil is more effective than conventional dosage form by protecting the prodrug from enzymatic attack which may further enhance the absorption leading to improved bioavailability, reduced dose and minimum side effects.

REFERENCES:

1. Castle SS. Cefpodoxime. Elsevier Inc, **2007**; 1:1-5.
2. Clough SR. Cefpodoxime In Editor-in-Chief: Philip W, Encyclopedia of Toxicology (Second Edition) New York: Elsevier, **2005**; 332-334.
3. Arora SC, Sharma PK, Khatar A, Gagoria J, Singh N and Irchhaiya R. Development,Characterization and Solubility Study of Cefpodoxime Proxetil by Solvent Evaporation Method, International Journal of ChemTech Research, **2010**; 2: 1156-1162.
4. Rao KS, Vairagkar RR Udgirkar DB, Patil PS and Biradar K. Development and Evaluation of Gastro retentive Floating Tablets of Cefpodoxime Proxetil, International Journal of Research in Pharmacy and Chemistry, **2012**; 2: 46-54.
5. Sahoo J, Murthy PN, Biswal S Avari JG and Girdkar RP. Enhancement of Dissolution of Gliclazide Using Solid Dispersions with Polyethylene glycol 6000, APPS Pharm. Sci. Tech., **2008**; 9: 563-571.
6. Shim JB, Kim MJ, Kim SJ and Kang SJ. Dissolution Properties of Controlled Released Solid Dispersion of Carvidol with HPMC and Eudragit RS. Journal of pharmaceutical investigation, **2012**; 4: 285-291.
7. Swamy MS. Development of New Analytical Method for Determination of Cefpodoxime Proxetil in Bulk Drug and in Pharmaceutical Formulation, **2010**; 1: 1-135.
8. Khan F, Katara R and Ramteke S. Enhancement of Bioavailability of Cefpodoxime Proxetil using different Polymeric Microparticles. American Association of Pharmaceutical Scientists PharmSciTech., **2010**; 11: 1-8.

9. Biswal S, Sahoo J, Murthy PN, Giradkar RP and Avari JG. Enhancement of Dissolution Rate of Gliclazide Using Solid Dispersions with Polyethylene Glycol 6000, American Association of Pharmaceutical Scientists PharmSciTech., **2008**; 9: 1-8.
10. Nimbalkar UA, Dhoka MV, Mane RB and Sonawane PA. Development and Characterization of Solid Dispersions of Cefpodoxime Proxetil with PEG 6000, International Research Journal of Pharmacy, **2011**; 5: 152-156.
11. Kushwaha A, Prajapati SK and Sharma B. Comparative Study of Acyclovir Solid Dispersion for Bioavailability Enhancement, American Journal of PharmTech Research, **2011**; 1: 180-201.

How to cite this article:

Bhupendra Kumar Poudel et al.,: Formulation and *In-Vitro* Evaluation of Gastro Retentive Tablets of Cefpodoxime Proxetil, J. Pharm. Res., 2015; 4(5): 201-205.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil